CELL BIOLOGY:

Signaling Vascular Morphogenesis and Maintenance

Douglas Hanahan

> ► Summary of this Article
> ► dEbates: Submit a response to this article
> ► Similar articles found in:
>   SCIENCE Online
> ► This Article has been cited by:
>   other online articles
> ► Search Medline for articles by:
>   Hanahan, D.
> ► Alert me when:
>   new articles cite this article
> ► Download to Citation Manager
>
> ► Collections under which this article appears:
>   Cell Biology

Blood vessels are constructed by two processes: vasculogenesis, whereby a primitive vascular network is established during embryogenesis from multipotential mesenchymal progenitors, and angiogenesis, in which preexisting vessels (both in embryo and adult) send out capillary sprouts to produce new vessels (1-3). Endothelial cells are centrally involved in each process: They migrate and proliferate and then assemble into tubes with tight cell-cell connections to contain the blood. Peri-endothelial support cells are recruited to encase the endothelial tubes, providing maintenance and modulatory functions to the vessels; such cells include pericytes for small capillaries, smooth muscle cells for larger vessels, and myocardial cells in the heart.

The establishment and remodeling of blood vessels is controlled by paracrine signals, many of which are protein ligands that bind and modulate the activity of transmembrane receptor tyrosine kinases (RTKs). This realization has emerged from the discovery and analysis of RTKs expressed on endothelial cells and of their ligands. Our basic view of RTK signaling has come from studies (performed largely in fibroblasts) of ligand-dependent autophosphorylation and activation of the branched Ras pathways. The results suggest that most RTKs are similarly coupled into the intracellular signal transduction cascade and are capable of inducing cell proliferation. However, the lessons from endothelial cells present a far more complicated picture. This complexity is highlighted by an article in this issue (4, page 55) of a ligand, called angiopoietin-2 (Ang2), that interferes with the kinase activity of an endothelial cell-selective RTK named Tie2. Remarkably, this inhibition of Tie2 kinase activity does not block endothelial cell proliferation and angiogenesis, but rather facilitates it.

Tie2 has two ligands, Ang1 and Ang2. Another major regulator of vasculogenesis and angiogenesis is vascular endothelial growth factor (VEGF, also called vascular permeability factor, VPF). VEGF signaling is itself mediated by two other endothelial cell-selective RTKs, called VEGF-R1 and VEGF-R2 (Flt1 and Flk1/KDR, respectively).

Mice carrying homozygous disruptions in the two highly homologous VEGF receptors die in mid-gestation of acute vascular defects, implicating each in vasculogenesis and developmental angiogenesis. However, the phenotypes are distinct--and instructive (see figure 1). VEGF-R2 knockout mice, which die by embryonic day 8.5 (E8.5), lack both endothelial cells and a developing hematopoietic system, implicating VEGF as a signal in the determination first of a hemato-angioblast progenitor and then of endothelial cells (5). In contrast, VEGF-R1 knockout mice, which also die around E8.5, have normal hematopoietic progenitors and abundant endothelial cells, which migrate and proliferate but do not assemble into tubes and functional vessels (6). Thus, these highly homologous RTKs send distinctive signals in endothelial cells.
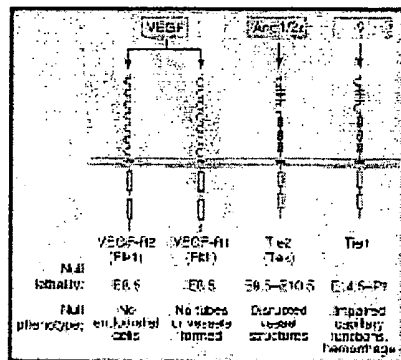

Fig. 1. Lessons from gene-knockout mice. The endothelial cell-selective RTKs VEGF-R1, VEGF-R2, Tie1, and Tie2 have all been ablated in gene-knockout mice. Each RTK knockout produced embryonic lethality with vascular defects. However, their distinctive phenotypes indicate that each of these tyrosine kinases controls a specific, complementary function in endothelial cells that collectively can account for a significant part of endothelial cell morphogenesis into functional vessels. See (22) for receptor structures.

Tie2 knockout mice die somewhat later in embryogenesis (E9.5 to E10.5). The Tie2 null phenotype is distinct from that of the VEGF receptor knockouts and is also informative. Endothelial cells are present in normal numbers and are assembled into tubes, but the vessels are immature, lacking branching networks and proper organization into large and small vessels (7, 8). There is also an absence of the angiogenesis that vascularizes the neuroectoderm by capillary sprouting from the primitive vascular network (or plexus). Notably, the vessels that do form lack an intimate encapsulation by peri-endothelial support cells. In the heart, the endocardium and myocardium do not show tight association and structural complexity; rather, the endocardial cells have aberrant, rounded shapes, are only loosely attached to the surrounding basement membrane, and in many locations are disconnected from myocardial cells. Similar defects in vessel architecture are evident in other tissues. Thus, the Tie2 tyrosine kinase appears to control the capability of endothelial cells to recruit stromal cells to encase the endothelial tubes so as to stabilize the structure and modulate the function of blood vessels.

The fourth endothelial cell-selective RTK, Tie1, remarkably similar in structure to Tie2 and appears to   ol another aspect of vessel integrity. Knockout mice lacking Tie1 die over a variable period, ranging from E14.5 to birth, of edema and hemorrhage, implicating the Tie1 signal in control of fluid exchange across capillaries and in hemodynamic stress resistance (8, 9).

New insights into the surprising concept that the Tie2 RTK is primarily coupled into a signal transduction circuit that elicits vessel maturation and maintains vessel integrity comes from functional analyses of the angiopoietins that bind to Tie2 and modulate its activity (4, 10, 11). The Tie2 ligands Ang1 and Ang2 are both ~75-kD secreted proteins with considerable sequence homology; each contains a coiled-coil and a fibrinogen-like domain. Both bind to the Tie2 receptor with similar affinity, and neither binds to the related receptor Tie1. Yet their effects on Tie2 are distinctive, as are their expression patterns in the mouse. Ang1 induces autophosphorylation of Tie2 in cultured endothelial cells. In marked contrast, Ang2, which binds with similar affinity, does not induce receptor phosphorylation. Rather, it can competitively inhibit Ang1-induced kinase activation of the Tie2 receptor. Thus Ang2 presents a negative signal to Tie2, a remarkable observation given its high homology to Ang1.

Moreover, this distinctive effect is apparently endothelial cell-specific. If a modified Tie2 is forcibly expressed in 3T3 fibroblasts, both Ang1 and Ang2 induce receptor phosphorylation and yet do not stimulate fibroblast proliferation. Similarly, Ang1-induced autophosphorylation of Tie2 does not affect endothelial cell growth in culture, consistent with the Tie2 knockout phenotype, which indicated that Tie2 is not required for endothelial cell proliferation during vasculogenesis. Functional studies in transgenic and gene-knockout mice support the notion that Ang1 signals Tie2 to recruit support cells, and that Ang2 inhibits this capability. Gene-knockout mice that lack Ang1 die with similar vascular defects to the Tie2 knockout mice (11). Transgenic mice overexpressing the negative ligand Ang2 in endothelial cells also die during embryogenesis, again with similar vascular defects (4). Thus, overexpression of Ang2 phenocopies loss of Ang1 expression, consistent with their opposite activities. Collectively, the data argue that Ang1 is the major physiological ligand for Tie2's functional role in recruiting and sustaining peri-endothelial support cells, whereas Ang2 serves to block this function, thereby relaxing these intimate and critical associations.

Why then does Ang2 exist? No doubt the Ang2 gene-knockout phenotype will prove illuminating. Meanwhile, the prevailing evidence suggests that Ang2 allows vascular remodeling, and in particular angiogenesis, processes that may be restricted by the encapsulation with basement membrane and peri-endothelial support cells. The clues come from the expression patterns of Ang1 and Ang2.

Ang1 is widely expressed both in the embryo and in the adult (4, 10). Ang2 is also widely expressed in the embryo. However, its expression pattern in the adult (in a limited survey) is provocative: Ang2 is selectively expressed in ovary, uterus, and placenta, the three tissues subject to physiological angiogenesis (4). The possible association of Ang2 with adult angiogenesis was investigated during ovulation, which is marked by distinctive phases of vascular quiescence, angiogenesis, and vascular regression. Ang2 expression in these stages was compared to that of Ang1 and VEGF. In early follicles, the vasculature is quiescent, and Ang1 is expressed, with little or no VEGF or Ang2 expression. In late pre-ovulatory follicles and in the postovulatory corpus luteum, where angiogenesis is ongoing, both VEGF and Ang2 are up-regulated, while Ang1 expression persists. Notably, Ang2 expression appears punctate, or focal. Finally, in nonproductive follicles, which show vascular regression, Ang2 is expressed at uniformly high levels, provocatively in the absence of VEGF expression.

These patterns of expression, when considered in the context of the lessons from the various gene-knockout phenotypes (see Fig. 1), collectively suggest a model for control of vasculogenesis, vessel maturation and maintenance, angiogenesis, and regression, as illustrated in Fig. 2. The Ang1/Tie2 circuit appears to mediate vessel maturation from simple endothelial tubes into more elaborate vascular structures composed of several cell types, and the maintenance of those vessels via the cell-cell and cell-matrix associations that produce them. Consequently, Ang1 may also help preserve endothelial cell quiescence. Focal expression of Ang2 evidently blocks the Ang1/Tie2 signal, resulting in a loosening of this tight vascular structure and thereby exposing the endothelial cells to activating signals from angiogenesis inducers, including VEGF. If VEGF (or another angiogenesis inducer) is present, the endothelial cells become activated to migrate and proliferate, producing new capillary sprouts and in turn tubes. One can envision that the more uniform presence of Ang1 allows a shift in the local balance of Ang1/Ang2 back in favor of Ang1, to effect maturation and stabilization of the newly formed vessels. Thus, there appears to be a collaboration between VEGF, Ang2, and Ang1 to elicit angiogenesis. In contrast, vascular regression is associated with very high-level expression of Ang2 in the absence of the activating (survival) signal from VEGF, presumably overwhelming the Ang1 signal and thereby producing catastrophic detachment from matrix and support cells, most likely with consequent apoptosis.

The work by Maisonpierre et al. (4) introduces an inhibitory ligand, Ang2, for the Tie2 regulatory RTK that normally helps maintain vascular integrity. A model is emerging of a regulatory mechanism through which blood vessels are constructed, maintained, remodeled, and eliminated. Other factors are also involved, during embryonic vasculogenesis and angiogenesis, and for physiological and pathological angiogenesis in the adult. For example, gene-knockout mice have also implicated a G protein-coupled receptor in vascular regulation, because in the absence of $G_{\alpha}13$, embryos die at E8.5 to E9.5, with defects in vascular assembly and angiogenesis (12). Moreover, a reciprocal paracrine signal has been revealed by gene-knockout mice that lack the genes for neuregulin, which is expressed in the endocardium of the heart, and the ErbB-2/3/4 RTKs, which are expressed in myocardium. Knockouts of this ligand or of its receptors produces defects in the developing heart analogous to those observed when Ang1 or Tie2 is missing (13-16). A similar role is suggested by gene-knockout mice for platelet-derived growth factor and its receptors in other tissue vasculature (17, 18). Furthermore, there is clear evidence in the adult for additional angiogenesis inducers and for an increasing number of angiogenesis inhibitors that act directly on endothelial cells (19-21). Thus, regulation of angiogenesis in ovulation and implantation, in wound healing, and in chronic pathological situations such as tumor progression will indeed be complex, but tractable using the power of animal models.
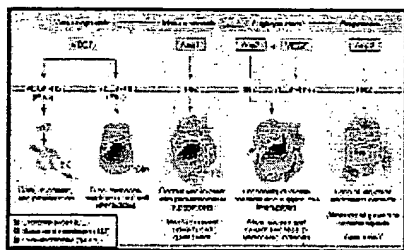

Fig. 2. Regulation of vascular morphogenesis, maintenance, and remodeling by RTKs and their ligands. A model for regulation of the vascular endothelium manifested by the prototypical angiogenesis factor VEGF and a new class of angiogenic regulators, Ang1 and Ang2. All three ligands bind to RTKs that have similar cytoplasmic signaling domains. Yet their downstream signals elicit distinctive cellular responses. Only VEGF binding to the VEGF-R2 sends a classical proliferative signal. When first activated in embryogenesis, this interaction induces the birth and proliferation of endothelial cells. In contrast, VEGF binding to VEGF-R1 elicits endothelial cell-cell interactions and capillary tube formation, a process that follows closely proliferation and migration of endothelial cells. Ang1 binding to the Tie2 RTK recruits and likely maintains association of peri-endothelial support cells (pericytes, smooth muscle cells, myocardiocytes), thus solidifying and stabilizing a newly formed blood vessel. The newly discovered Ang2, although highly homologous to Ang1, does not activate the Tie2 RTK; rather, it binds and blocks kinase activation in endothelial cells. The Ang2 negative signal causes vessel structures to become loosened, reducing endothelial cell contacts with matrix and disassociating peri-endothelial support cells. This loosening appears to render the endothelial cells more accessible and responsive toward the angiogenic inducer VEGF (and likely to other inducers). Finally, Ang2 is expressed at uniformly high levels in vascular regression in nonproductive ovarian follicles; the lack of VEGF coexpression suggests that loosening of cell-matrix interactions in the absence of a growth or survival signal elicits endothelial cell death, likely by apoptosis. No doubt additional factors play into these distinctive states, including the emerging class of

.angiogenesis inhibitors that directly block endot   cell proliferation and migration.

Illustration: K. Sutliff

That complexity notwithstanding, the evidence is compelling that VEGF and the angiopoietins, and their cognate receptors, are critical components of the vascular regulatory machinery. It will be of particular interest to establish the possible contributions of Ang2 to tumor angiogenesis, whereby the quiescent vasculature (likely maintained in part by Ang1/Tie2) is activated to elicit and chronically effect the angiogenic phenotype that accompanies tumor growth and metastasis. Ang2 could well serve as an initial angiogenic signal, locally opening up the vessel structure to allow protease degradation of the basement membrane surrounding the endothelium and accessibility to that endothelium by angiogenesis inducers such as VEGF, thereby eliciting capillary sprouting and in turn new blood vessels that sustain a tumor as it expands.

References and Notes

1. W. Risau and I. Flamme, *Annu. Rev. Cell Dev. Biol.* **11**, 73 (1995) [Medline].
2. J. Folkman and P. A. D'Amore, *Cell* **87**, 1153 (1996) [Medline].
3. W. Risau, *Nature* **386**, 671 (1997) [Medline].
4. P. C. Maisonpierre *et al.*, *Science* **277**, 55 (1997).
5. F. Shalaby *et al.*, *Nature* **376**, 62 (1995) [Medline].
6. G.-H. Fong, J. Rossant, M. Gertsenstein, M. L. Breitman, *ibid.*, p. 66[Medline].
7. D. J. Dumont *et al.*, *Genes Dev.* **8**, 1897 (1994) [Medline].
8. T. Sato *et al.*, *Nature* **376**, 70 (1995) [Medline].
9. M. C. Puri, J. Rossant, K. Alitalo, A. Bernstein, J. Partanen, *EMBO J.* **14**, 5884 (1995) [Medline].
10. S. Davis *et al.*, *Cell* **87**, 1161 (1996) [Medline].
11. C. Suri *et al.*, *ibid.*, p. 1171[Medline].
12. S. Offermanns, V. Mancino, J.-P. Revel, M. I. Simon, *Science* **275**, 533 (1997).
13. K.-F. Lee *et al.*, *Nature* **378**, 394 (1995) [Medline].
14. M. Gassmann *et al.*, *ibid.*, p. 390[Medline].
15. D. Meyer and C. Birchmeier, *ibid.*, p. 386[Medline].
16. R. Kramer *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 4833 (1996) [Medline].
17. P. Leveen *et al.*, *Genes Dev.* **8**, 1875 (1994) [Medline].
18. P. Soriano, *ibid.*, p. 1888[Medline].
19. N. Bouck, V. Stellmach, S. Hsu, *Adv. Cancer Res.* **69**, 135 (1996) [Medline].
20. J. Folkman, in *The Molecular Basis of Cancer*, J. Mendelsohn, P. M. Howley, M. A. Israel, L. A. Liotta, Eds. (Saunders, Philadelphia, 1995), vol. 9, pp. 206-232.
21. D. Hanahan and J. Folkman, *Cell* **86**, 353 (1996) [Medline].
22. T. Mustonen and K. Alitalo, *J. Cell Biol.* **129**, 895 (1995) [Medline].
23. I thank E. Bergsland, G. Bergers, D. Jackson, and W. Risau for helpful comments.

The author is in the Department of Biochemistry and Biophysics and the Hormone Research Insti-tute, University of California at San Francisco, San Francisco, CA 94143-0534, USA. E-mail: doug_hanahan@biochem.ucsf.edu

This article has been cited by other articles:

- Robert, B., St. John, P. L., Abrahamson, D. R. (1998). Direct visualization of renal vascular morphogenesis in Flk1 heterozygous mutant mice. *Am. J. Physiol.* 275: 164-172 [Abstract] [Full Text]
- Neely, K. A., Gardner, T. W. (1998). Ocular Neovascularization : Clarifying Complex Interactions. *Am J Pathol* 153: 665-670 [Full Text]
- Laurén, J., Gunji, Y., Alitalo, K. (1998). Is Angiopoietin-2 Necessary for the Initiation of Tumor Angiogenesis?. *Am J Pathol* 153: 1333-1339 [Full Text]
- Stratmann, A., Risau, W., Plate, K. H. (1998). Cell Type-Specific Expression of Angiopoietin-1 and Angiopoietin-2 Suggests a Role in Glioblastoma Angiogenesis. *Am J Pathol* 153: 1459-1466 [Abstract] [Full Text]
- Theurillat, J.-P., Hainfellner, J., Maddalena, A., Weissenberger, J., Aguzzi, A. (1999). Early Induction of Angiogenetic Signals in Gliomas of GFAP-v-src Transgenic Mice. *Am J Pathol* 154: 581-590 [Abstract] [Full Text]
- O'Donnell, K., Harkes, I. C., Dougherty, L., Wicks, I. P. (1999). Expression of Receptor Tyrosine Kinase Axl and its Ligand Gas6 in Rheumatoid Arthritis : Evidence for a Novel Endothelial Cell Survival Pathway. *Am J Pathol* 154: 1171-1180 [Abstract] [Full Text]
- Crosby, J. R., Tappan, K. A., Seifert, R. A., Bowen-Pope, D. F. (1999). Chimera Analysis Reveals That Fibroblasts and Endothelial Cells Require Platelet-Derived Growth Factor Receptorβ Expression for Participation in Reactive Connective Tissue Formation in Adults but Not during Development. *Am J Pathol* 154: 1315-1321 [Abstract] [Full Text]
- Pinter, E., Mahooti, S., Wang, Y., Imhof, B. A., Madri, J. A. (1999). Hyperglycemia-Induced Vasculopathy in the Murine Vitelline Vasculature : Correlation with PECAM-1/CD31 Tyrosine Phosphorylation State. *Am J Pathol* 154: 1367-1379 [Abstract] [Full Text]
- Mandriota, S. J., Pyke, C., Di Sanza, C., Quinodoz, P., Pittet, B., Pepper, M. S. (2000). Hypoxia-Inducible Angiopoietin-2 Expression Is Mimicked by Iodonium Compounds and Occurs in the Rat Brain and Skin in Response to Systemic Hypoxia and Tissue Ischemia. *Am J Pathol* 156: 2077-2089 [Abstract] [Full Text]
- Dunk, C., Shams, M., Nijjar, S., Rhaman, M., Qiu, Y., Bussolati, B., Ahmed, A. (2000). Angiopoietin-1 and Angiopoietin-2 Activate Trophoblast Tie-2 to Promote Growth and Migration during Placental Development. *Am J Pathol* 156: 2185-2199 [Abstract] [Full Text]
- Mitzner, W., Lee, W., Georgakopoulos, D., Wagner, E. (2000). Angiogenesis in the Mouse Lung. *Am J Pathol* 157: 93-101 [Abstract] [Full Text]
- Tempel, C., Gilead, A., Neeman, M. (2000). Hyaluronic Acid as an Anti-Angiogenic Shield in the Preovulatory Rat Follicle. *Biol Reprod* 63: 134-140 [Abstract] [Full Text]
- Hirashima, M., Kataoka, H., Nishikawa, S., Matsuyoshi, N., Nishikawa, S.-I. (1999). Maturation of Embryonic Stem Cells Into Endothelial Cells in an In Vitro Model of Vasculogenesis. *Blood* 93: 1253-1263 [Abstract] [Full Text]
- Nie, D., Tang, K., Diglio, C., Honn, K. V. (2000). Eicosanoid regulation of angiogenesis: role of endothelial arachidonate 12-lipoxygenase. *Blood* 95: 2304-2311 [Abstract] [Full Text]
- Kubo, H., Fujiwara, T., Jussila, L., Hashi, H., Ogawa, M., Shimizu, K., Awane, M., Sakai, Y., Takabayashi, A., Alitalo, K., Yamaoka, Y., Nishikawa, S.-I. (2000). Involvement of vascular endothelial growth factor receptor-3 in maintenance of integrity of endothelial cell lining during tumor angiogenesis. *Blood* 96: 546-553 [Abstract] [Full Text]

- Kerbel, R. S. (2000). Tumor angiogenes... ast, present and the near future. *Carcinogenesis* 21 ...-515 [Abstract] [Full Text]
- Risau, W. (1998). Angiogenesis Is Coming of Age. *Circulation Research* 82: 926-928 [Full Text]
- Asahara, T., Chen, D., Takahashi, T., Fujikawa, K., Kearney, M., Magner, M., Yancopoulos, G. D., Isner, J. M. (1998). Tie2 Receptor Ligands, Angiopoietin-1 and Angiopoietin-2, Modulate VEGF-Induced Postnatal Neovascularization. *Circulation Research* 83: 233-240 [Abstract] [Full Text]
- Peters, K. G. (1998). Vascular Endothelial Growth Factor and the Angiopoietins : Working Together to Build a Better Blood Vessel. *Circulation Research* 83: 342-343 [Full Text]
- Mandriota, S. J., Pepper, M. S. (1998). Regulation of Angiopoietin-2 mRNA Levels in Bovine Microvascular Endothelial Cells by Cytokines and Hypoxia. *Circulation Research* 83: 852-859 [Abstract] [Full Text]
- Kim, I., Kim, H. G., Moon, S. O., Chae, S. W., So, J. N., Koh, K. N., Ahn, B. C., Koh, G. Y. (2000). Angiopoietin-1 Induces Endothelial Cell Sprouting Through the Activation of Focal Adhesion Kinase and Plasmin Secretion. *Circulation Research* 86: 952-959 [Abstract] [Full Text]
- Willam, C., Koehne, P., Jürgensen, J. S., Gräfe, M., Wagner, K. D., Bachmann, S., Frei, U., Eckardt, K.-U. (2000). Tie2 Receptor Expression Is Stimulated by Hypoxia and Proinflammatory Cytokines in Human Endothelial Cells. *Circulation Research* 87: 370-377 [Abstract] [Full Text]
- Rosengart, T. K., Lee, L. Y., Patel, S. R., Sanborn, T. A., Parikh, M., Bergman, G. W., Hachamovitch, R., Szulc, M., Kligfield, P. D., Okin, P. M., Hahn, R. T., Devereux, R. B., Post, M. R., Hackett, N. R., Foster, T., Grasso, T. M., Lesser, M. L., Isom, O. W., Crystal, R. G. (1999). Angiogenesis Gene Therapy : Phase I Assessment of Direct Intramyocardial Administration of an Adenovirus Vector Expressing VEGF121 cDNA to Individuals With Clinically Significant Severe Coronary Artery Disease. *Circulation* 100: 468-474 [Abstract] [Full Text]
- Shyu, K.-G., Manor, O., Magner, M., Yancopoulos, G. D., Isner, J. M. (1998). Direct Intramuscular Injection of Plasmid DNA Encoding Angiopoietin-1 but not Angiopoietin-2 Augments Revascularization in the Rabbit Ischemic Hindlimb. *Circulation* 98: 2081-2087 [Abstract] [Full Text]
- MIOSGE, N., SASAKI, T., TIMPL, R. (1999). Angiogenesis inhibitor endostatin is a distinct component of elastic fibers in vessel walls. *FASEB J.* 13: 1743-1750 [Abstract] [Full Text]
- Pereira, F. A., Qiu, Y., Zhou, G., Tsai, M.-J., Tsai, S. Y. (1999). The orphan nuclear receptor COUP-TFII is required for angiogenesis and heart development. *Genes & Dev.* 13: 1037-1049 [Abstract] [Full Text]
- Gale, N. W., Yancopoulos, G. D. (1999). Growth factors acting via endothelial cell-specific receptor tyrosine kinases: VEGFs, Angiopoietins, and ephrins in vascular development. *Genes & Dev.* 13: 1055-1066 [Full Text]
- Krebs, L. T., Xue, Y., Norton, C. R., Shutter, J. R., Maguire, M., Sundberg, J. P., Gallahan, D., Closson, V., Kitajewski, J., Callahan, R., Smith, G. H., Stark, K. L., Gridley, T. (2000). Notch signaling is essential for vascular morphogenesis in mice. *Genes & Dev.* 14: 1343-1352 [Abstract] [Full Text]
- Kohnen, G., Campbell, S., Jeffers, M. D., Cameron, I. T. (2000). Spatially regulated differentiation of endometrial vascular smooth muscle cells. *Hum Reprod* 15: 284-292 [Abstract] [Full Text]
- Ruoslahti, E., Rajotte, D. (2000). An Address System in the Vasculature of Normal Tissues and Tumors. *Annu. Rev. Immunol.* 18: 813-827 [Abstract] [Full Text]
- Otani, A., Takagi, H., Oh, H., Koyama, S., Matsumura, M., Honda, Y. (1999). Expressions of Angiopoietins and Tie2 in Human Choroidal Neovascular Membranes. *Invest. Ophthalmol. Vis. Sci.* 40: 1912-1920 [Abstract] [Full Text]
- Baffi, J., Byrnes, G., Chan, C.-C., Csaky, K. G. (2000). Choroidal Neovascularization in the Rat Induced by Adenovirus Mediated Expression of Vascular Endothelial Growth Factor. *Invest. Ophthalmol. Vis. Sci.* 41: 3582-3589 [Abstract] [Full Text]
- Hayashi, K.'i., Saga, H., Chimori, Y., Kimura, K., Yamanaka, Y., Sobue, K. (1998). Differentiated Phenotype of Smooth Muscle Cells Depends on Signaling Pathways through Insulin-like Growth Factors and Phosphatidylinositol 3-Kinase. *J. Biol. Chem.* 273: 28860-28867 [Abstract] [Full Text]
- Davis-Smyth, T., Presta, L. G., Ferrara, N. (1998). Mapping the Charged Residues in the Second Immunoglobulin-like Domain of the Vascular Endothelial Growth Factor/Placenta Growth Factor Receptor Flt-1 Required for Binding and Structural Stability. *J. Biol. Chem.* 273: 3216-3222 [Abstract] [Full Text]
- Huang, L., Sankar, S., Lin, C., Kontos, C. D., Schroff, A. D., Cha, E. H., Feng, S.-M., Li, S.-F., Yu, Z., Van Etten, R. L., Blanar, M. A., Peters, K. G. (1999). HCPTPA, a Protein Tyrosine Phosphatase That Regulates Vascular Endothelial Growth Factor Receptor-mediated Signal Transduction and Biological Activity. *J. Biol. Chem.* 274: 38183-38188 [Abstract] [Full Text]
- Papapetropoulos, A., Fulton, D., Mahboubi, K., Kalb, R. G., O'Connor, D. S., Li, F., Altieri, D. C., Sessa, W. C. (2000). Angiopoietin-1 Inhibits Endothelial Cell Apoptosis via the Akt/Survivin Pathway. *J. Biol. Chem.* 275: 9102-9105 [Abstract] [Full Text]
- Kanda, S., Lerner, E. C., Tsuda, S., Shono, T., Kanetake, H., Smithgall, T. E. (2000). The Nonreceptor Protein-tyrosine Kinase c-Fes Is Involved in Fibroblast Growth Factor-2-induced Chemotaxis of Murine Brain Capillary Endothelial Cells. *J. Biol. Chem.* 275: 10105-10111 [Abstract] [Full Text]
- (1998). Fallen Arches, or How the Vertebrate Got Its Head. *J. Clin. Invest.* 102: 1-3 [Full Text]
- Tanaka, S., Mori, M., Sakamoto, Y., Makuuchi, M., Sugimachi, K., Wands, J. R. (1999). Biologic significance of angiopoietin-2 expression in human hepatocellular carcinoma. *J. Clin. Invest.* 103: 341-345 [Abstract] [Full Text]
- Yamagishi, H., Olson, E. N., Srivastava, D. (2000). The basic helix-loop-helix transcription factor, dHAND, is required for vascular development. *J. Clin. Invest.* 105: 261-270 [Abstract] [Full Text]
- Liu, Y., Wada, R., Yamashita, T., Mi, Y., Deng, C.-X., Hobson, J. P., Rosenfeldt, H. M., Nava, V. E., Chae, S.-S., Lee, M.-J., Liu, C. H., Hla, T., Spiegel, S., Proia, R. L. (2000). Edg-1, the G protein-coupled receptor for sphingosine-1-phosphate, is essential for vascular maturation. *J. Clin. Invest.* 106: 951-961 [Abstract] [Full Text]
- Ashkar, A. A., Di Santo, J. P., Croy, B. A. (2000). Interferon {gamma} Contributes to Initiation of Uterine Vascular Modification, Decidual Integrity, and Uterine Natural Killer Cell Maturation during Normal Murine Pregnancy. *J. Exp. Med.* 192: 259-270 [Abstract] [Full Text]
- Kontos, C. D., Stauffer, T. P., Yang, W.-P., York, J. D., Huang, L., Blanar, M. A., Meyer, T., Peters, K. G. (1998). Tyrosine 1101 of Tie2 Is the Major Site of Association of p85 and Is Required for Activation of Phosphatidylinositol 3-Kinase and Akt. *Mol. Cell . Biol.* 18: 4131-4140 [Abstract] [Full Text]
- Hazzard, T.M., Molskness, T.A., Chaffin, C.L., Stouffer, R.L. (1999). Vascular endothelial growth factor (VEGF) and angiopoietin regulation by gonadotrophin and steroids in macaque granulosa cells during the peri-ovulatory interval. *Mol Hum Reprod* 5: 1115-1121 [Abstract] [Full Text]
- Goldman-Wohl, D. S., Ariel, I., Greenfield, C., Lavy, Y., Yagel, S. (2000). Tie-2 and angiopoietin-2 expression at the fetal-maternal interface: a receptor ligand model for vascular remodelling. *Mol Hum Reprod* 6: 81-87 [Abstract] [Full Text]
- Daniel, T. O., Abrahamson, D. (2000). Endothelial Signal Integration in Vascular Assembly. *Annu. Rev. Physiol.* 62: 649-71 [Abstract] [Full Text]
- Jiang, B.-H., Zheng, J. Z., Aoki, M., Vogt, P. K. (1900). Phosphatidylinositol 3-kinase signaling mediates angiogenesis and expression of vascular endothelial growth factor in endothelial cells. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.0/2000/040560897
- Jiang, B.-H., Zheng, J. Z., Aoki, M., Vogt, P. K. (2000). Phosphatidylinositol 3-kinase signaling mediates angiogenesis and expression of vascular endothelial growth factor in endothelial cells. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.040560897 [Abstract] [Full Text]
- Schechner, J. S., Nath, A. K., Zheng, L., Kluger, M. S., Hughes, C. C. W., Sierra-Honigmann, M. R., Lorber, M. I., Tellides, G., Kashgarian, M., Bothwell, A. L. M., Pober, J. S. (2000). In vivo formation of complex microvessels lined by human endothelial cells in an immunodeficient mouse. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.150242297v1 [Abstract] [Full Text]
- Valenzuela, D. M., Griffiths, J. A., Rojas, J., Aldrich, T. H., Jones, P. F., Zhou, H., McClain, J., Copeland, N. G., Gilbert, D. J., Jenkins, N. A., Huang, T., Papadopoulos, N., Maisonpierre, P. C., Davis, S., Yancopoulos, G. D. (1999). Angiopoietins 3 and 4: Diverging gene counterparts in mice and humans. *Proc. Natl. Acad. Sci. U. S. A.* 96: 1904-1909 [Abstract] [Full Text]
- Schechner, J. S., Nath, A. K., Zheng, L., Kluger, M. S., Hughes, C. C. W., Sierra-Honigmann, M. R., Lorber, M. I., Tellides, G., Kashgarian, M., Bothwell, A. L. M., Pober, J. S. (2000). In vivo formation of complex microvessels lined by human endothelial cells in an immunodeficient mouse. *Proc. Natl. Acad. Sci. U. S. A.* 97: 9191-9196 [Abstract] [Full Text]
- Jiang, B.-H., Zheng, J. Z., Aoki, M., Vogt, P. K. (2000). Phosphatidylinositol 3-kinase signaling mediates angiogenesis and expression of vascular endothelial growth factor in endothelial cells. *Proc. Natl. Acad. Sci. U. S. A.* 97: 1749-1753 [Abstract] [Full Text]
- Arap, W., Pasqualini, R., Ruoslahti, E. (1998). Cancer Treatment by Targeted Drug Delivery to Tumor Vasculature in a Mouse Model. *Science* 279: 377-380 [Abstract] [Full Text]

- Thurston, G., Suri, C., Smith, K., McC___, J., Sato, T. N., Yancopoulos, G. D., McDonald, D. ___ (1999). Leakage-Resistant Blood Vessels in Mice Transgenically Overexpressing Angiopoietin-1. *Science* 286: 2511-2514 [Abstract] [Full Text]

▲ PAGE TOP